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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/457,926	CHRISTENSEN ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-46,49-51,53-55,57 and 58* is/are pending in the application.

4a) Of the above claim(s) *42,44-46,57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41, 43, 49-51 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 41-46, 49-51, 53-55, 57 and 58 are pending. Claims 42, 44-46, 57 and 58 are withdrawn from consideration. Claims 41, 43, 49-51 and 53-55 are examined.

Election/Restrictions

2. The restriction and requirement for election of species, as set forth in the Requirement for Restriction/Election mailed 2/20/2001, and applicant's election of Group I, originally claims 41-55 and of species 2 of beta-lactam antibiotic, formula (b), (claims 43, 53 and 54), Vancomycin, and the linkage set forth in claim 49, entered 3/19/2001, is maintained.

3. Claims 42, 44-46, 57 and 58 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species, there being no allowable generic claim. See below rejection under 35 USC 103(a).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 41, 43, 49-51 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Truett (US 5,693,791; on PTO-1449) in view of Truett (US 6,437,119, IDS filed 12/1/2004, priority to May 7, 1998); and Boeckh et al (Antimicrob. Agents Chemother., 1988, Vol. 32, No. 1, pp. 92-95; of record) and Renoud-Grappin et al

(Antiviral Chem. and Chemotherapy, Vol. 9, No.3, 1998, pp. 205-221, of record) and Staroske et al (Tet. Lett., 1998, Vol. 39; on PTO-1449). This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is reproduced below.

Truett, US 5,693,791, teaches the "linking of diverse antibiotic moieties via difunctional organic compounds" (see column 1, lines 8-9). Specifically, dimers are taught having the structure A-L-B, where A and B are various antibiotic moieties (see "Summary", columns 1-6, especially column 1, lines 46-64). A variety of linkers and linkage chemistries are taught (see columns 25-32). The reference teaches that the linkage of two antibiotic moieties can create compounds of new activity (see column 1, lines 1-30) and that "two antibiotic moieties can be linked in which one is known to attack Gram positive bacteria and another to attack Gram negative bacteria" (see column 1, lines 27-30). Truett teaches a dimeric compound where one of the antibiotic moieties is ceftazidime (see column 3, line 7). Ceftazidime is a beta lactam antibiotic that reads on the elected species that is set forth in claim 53, see structure in the instant Figure 6B-2. Truett lacks the teaching of linking vancomycin with ceftazidime.

Truett, US 6,437,119, throughout the patent and abstract, teaches linking antibiotics by internal reactions to give three linked antibiotics for controlling infections via suppressing DNA replication, cell wall formation and protein synthesis. Truett, US 6,437,119, at col. 1, lines 12-21, col. 2, lies 26-34, col. 2, line 65-col. 3, line 47, and col. 26, lines 48-56, teach that making and using compounds having three antibiotic functionalities linked together, where a quinolone derivative is linked to a beta-lactam, which, in turn, is linked to vancomycin. Thus Truett, US 6,437,119 teaches linking a beta-lactam antibiotic to vancomycin in an antibiotic compound. Truett, US 6,437,119, is a continuation in part of US Application No. 09/304,715, filed 5/4/1999, and claims benefit of Provisional Application No. 60/084,586, filed 5/7/1998.

It was well known in the art at the time of filing to use combination therapy with vancomycin and ceftazidime. For example, **Boeckh et al** teach that this combination therapy is used to "cover a broad spectrum of gram positive and gram negative bacteria-- (see page 92, first paragraph). The reference teaches the pharmacokinetics of the combination of vancomycin and ceftazidime, administered to humans (see Abstract and Table 1), thus pharmaceutical compositions of the drugs are well known.

Renoud-Grappin et al teach that one way to achieve effective combination therapy is to covalently link two different drugs. See page 208, first column, first full paragraph of the reference, which describes using heterodimers for combination therapy linked "through an appropriate spacer, in an attempt to combine the inhibitory capacity" of two different classes of molecules. The reference also describes that one would attempt such an approach to span two binding sites on the target. Renoud-Grappin et al also discuss combining different drugs to "prevent the emergence of drug-resistant virus strains" and set forth three main reasons for combination therapy (see page 207, 2nd column, 2nd paragraph. It is recognized that the linked compounds of Renoud-Grappin et al (see, for example, Figure 4 of the reference) are anti-virals and not antibiotics; however, it is the examiner's position that one of ordinary skill would recognize the relevance of preventing the emergence of drug-resistant strains for both classes of molecules since such was well established in the art.

Additionally, vancomycin dimers were also known in the art at the time of filing. **Staroske et al** discuss both "head-to-head" and "head-to-tail" dimers (see Figure 3) and that in "light of recent reports of vancomycin-resistant bacteria" there is a "strong incentive for the development of more potent antibiotics" (page 4917, bottom). The reference also teaches that dimeric vancomycin compounds exhibit improved antibacterial activity, see for example, page 4918, top. Specifically, the dimers of Staroske et al are linked from the amino terminus of one vancomycin moiety to the carboxy terminus of another (see

Scheme 1, page 4919). The reference also contemplates linking of the vancomycin at the vancosamine moiety (see page 4920, last two paragraphs).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to link vancomycin and ceftazidime, based on the teaching of Truett, US 5,693,791, concerning the linking of diverse antibiotic moieties, and Truett US 6,437,119, where vancomycin and beta-lactam antibiotics are linked as part of a linked, three antibiotic compound, combined with the teaching of Boeckh et al to perform combination therapy using the drugs, the teaching of Renoud-Grappin concerning linking drugs to perform combination therapy and the teaching of Staroske et al concerning vancomycin dimers linked through the amino and carboxy terminus. Specifically, the references of Truett, US 5,693,791, teach that two antibiotics, one known to attack Gram positive bacteria and another to attack Gram negative bacteria can be linked and the advantages of doing such, and Boeckh et al teach that vancomycin and ceftazidime fulfill these requirements. Furthermore, Truett US 6,437,119, teaches linking vancomycin and a beta-lactam as part of a three compound antibiotic. Renoud-Grappin teaches that one way to achieve effective combination therapy is to covalently link two different drugs. Finally, Staroske et al teach that vancomycin can be linked at specific linkage sites.

One of ordinary skill would have been motivated to covalently link vancomycin with ceftazidime to create a broad spectrum antibiotic compound to fight antibiotic resistant strains. Furthermore, it would have been obvious for one of ordinary skill in the art to have combined the compounds taught by the references of Truett, US 5,693,791 and Truett US 6,437,119, because said compounds are used for a common purpose, i.e., the treatment of bacterial infection. See In re Kerhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (stating: "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art" [citations omitted]); and MPEP 2144.06.

One of ordinary skill would also have had a reasonable expectation of success based on the fact that the references of Truett, US 5,693,791 and Truett US 6,437,119 and Staroske et al teach linking chemistry for vancomycin and beta-lactam compounds.

Applicant, in the Reply entered 6/28/2005, at p. 6, for example, argues that a prima facie case of obvious has not been established because there exists neither suggestion nor motivation to combine and modify the five references relied upon in the rejection in the manner proposed by the Examiner", (Reply at p. 6).

In Section 1, in regards to the reference of Truett, US 5,693,791, which applicant refers to as Truett I, applicant argues that the examiner must provide a basis for the initial selection of a single one of the 69 specific compounds (distributed among 9 classes of compounds) disclosed in Truett I, i.e., ceftazidime, from among all the other antibiotic compounds disclosed in the reference. Applicant argues that "after consideration of the teaching of Truett I as a whole, the reference does not contain the

specific guidance needed to suggest the selection of ceftazidime over all the other disclosed antibiotics", (Reply at p. 7, para 3).

Applicant argues that that Truett I "was filed at a time when vancomycin was well-known in the art, i.e., 1995, yet fails to mention vancomycin or even the general class of antibiotics to which it belongs. Applicants therefore submit that a reading of Truett I as a whole would not have motivated one skilled in the art to modify Truett I to combine vancomycin with any of the 9 disclosed classes of antibiotics, let alone combine vancomycin with ceftazidime, one of the 69 specifically disclosed compounds, in an attempt to arrive at the presently claimed invention." Reply at p. 8.

In Section 2, in regards to the reference of Truett, US 6,437,119, which applicant refers to as Truett II, applicant argues that, "Truett II, at best, discloses the linking of a third antibiotic, such as vancomycin, to a bicomponent compound that already contains a quinolone moiety linked to a beta-lactam moiety. Such a disclosure can be found, for example, at col. 3, lines 55-65 of Truett II, in the description of the synthesis of the general formula

Q—CONH—B—C(O)—Z—A

where Q is a quinolone, B is a beta lactam, and A is a third antibiotic, such as vancomycin."

Applicant argues that neither Truett I, nor the examiner, is concerned with the addition of a third antibiotic moiety to any of the bi-component compounds that may be

produced according to the disclosure of Truett I. Applicant states that the examiner has suggested the substitution of one of the moieties of Truett I with one of the third moieties disclosed in Truett II. Applicant states that by removing one of the moieties in Truett II, the composition of three antibiotics, which is the focus of the reference, would be destroyed. Applicant argues that Truett II teaches linking vancomycin to ceftazidime, but only in the where vancomycin is simultaneously linked to a third antibiotic.

In Section 3, applicant argues that reliance upon *In re Kerhoven, 626 F.2d 846*, (C.C.P.A. 1980) is misplaced. Applicant argues that the examiner does not combine compositions, but is picking and choosing individual components from isolated disclosures. Applicant argues that the examiner erroneously believes that any combination of antibiotic moieties in every antibiotic composition is obvious so long as each individual moiety is found in that art.

Applicant distinguishes *In re Kerkhoven*, arguing that it was the "mere mixture" of the two detergent compositions that were at issue in *In re Kerhoven*; in the present case, the claims involve the linking of different moieties to produce a new compound, and this linking would involve chemical reactions. Therefore, the incorrect extrapolation of the holding in *In* re Kerkhoven amounts to nothing less than another application of the impermissible "obvious to try" standard.

In Section 4, applicant argues that the three references of Boeckh, Renoud-Grappin, and Staroske, fail to remedy the deficiencies of Truett I and Truett II. For

example, nothing in any of Boeckh, Renoud-Grappin, and Staroske would have led one of ordinary skill in the art away from the direct teachings in Truett II to employ a three-component antibiotic compound.

Response to Arguments

Applicant's arguments filed 6/28/2005 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The reply to the previous Office action, entered 6/28/2005, applicant argues that the references must be considered as a whole. The examiner respectfully submits that applicant's arguments, in actuality, do not do this. The references, taken as a whole, teach and suggest heteromers of antibiotic compounds. Truett, in Truett I, teaches that the linking of two antibiotic moieties functioning in different and states:

> It has been realized that the linking of two antibiotic moieties functioning in different fashions, as for example inhibiting cell-wall synthesis or protein synthesis or DNA synthesis, can be of value. Two antibiotic moieties can also be linked in which one is known to attack Gram positive bacteria and another to attack Gram negative bacteria, and this new entity is of value.

Truett I, at col. 1, lines 24-30. Truett, in the later patent Truett II, teaches compositions of three linked antibiotics, and states:

> The value of a composition wherein a trio of individual antibiotics are joined is that the bacterial infective agent will simultaneously be attacked by agents which are known to attack the cell-wall producing enzyme of the bacteria, and inhibit the DNA gyrase enzyme, and inhibit the enzyme that controls bacterial protein synthesis.

Truett II, at col. 1, lines 21-27. Thus the motivation for using heterodimeric antibiotic compounds of Truett I is closely related and extendable to the heterotrimeric antibiotic compounds of related patent Truett II.

The reference of Truett I teaches and suggests the use of ceftazidime as a member antibiotic of a dimeric compound. Truett I, at col. 2, line 3-col. 3, line 14 lists cephalosporins and related compounds as suitable for inclusion in dimeric antibiotic compounds. Truett I includes naming ceftazidime as a cephalosporins "of particular interest", (Truett I at col. 2, line 60) and provides the structure of ceftazidime, (Truett I at col. 15, lines 1-15). Thus Truett I provides ample motivation for the selection of ceftazidime. Furthermore, one of ordinary skill in the art would be motivated to use ceftazidime in the heteromeric antibiotic compounds as taught by Truett, because ceftazidime was a recognized antibiotic drug with demonstrated efficacy. Also, the examiner respectfully submits that would one of ordinary skill in the art would be motivated to use any or all of the 69 specifically disclosed compounds of the 9 disclosed classes of antibiotics, and vancomycin, because of their predictable efficacy as recognized drugs and because 69 specific, known compounds does not represent an unreasonable number, in and of itself, to use in the claimed invention of the prior art reference of Truett I.

The examiner respectfully submits that applicant's argument that that Truett I "was filed at a time when vancomycin was well-known in the art, i.e., 1995, yet fails to mention vancomycin or even the general class of antibiotics to which it belongs," is a further example of attacking the references individually, because another prior art reference, that of Truett II, explicitly teaches vancomycin prior to the filing date of the instant application. Whether vancomycin was well known as of the date that the particular reference of Truett I was filed or published is not relevant to the instant rejection for obviousness. The prior art reference of Truett II taught a trimeric antibiotic compound where vancomycin is linked to a lactam, such as a cephalosporin. The reference of Boeckh et al. taught that vancomycin, in combination with ceftazidime, was frequently to cover a broad spectrum of gram-positive and gram-negative bacteria in serious infections in neutropenic cancer patients, (Boeckh et al. at p. 92, para 1 and p. 94, para 4). This relates to Truett I teaching of linking two different antibiotics in order to target both gram-positive and gram-negative bacteria. Boeckh et al. at p. 94, para 4, states: "In summary, the combination of vancomycin and ceftazidime is an effective regimen to compensate for the poor antistaphylococcal activity of ceftazidime alone", (citation omitted). The reference of Staroske et al. teaches synthesis of covalent homodimers of vancomycin. Thus vancomycin, vancomycin covalently linked to cephalosporins, administration of a combination of vancomycin and ceftazidime, as well as dimers of vancomycin were taught and suggested in the prior art at the time the claimed invention was made.

Thus the combination and linking of vancomycin and cephalosporins, and well as the particular cephalosporin, ceftazidime, (as taught by Truett II and Boeckh et al.), are taught by the prior art. One of ordinary skill in the art would have been motivated to link vancomycin with ceftazidime, as taught by the prior art as taught by Truett II, to form a heterodimeric antibiotic compound comprising a cephalosporin, such as ceftazidime, and as taught by Truett I, to create a composition of ceftazidime and vancomycin for use as a broad spectrum antibiotic effective against gram-positive and gram-negative bacteria, as suggested by both Truett I and Truett II, by and Boeckh et al. One of ordinary skill in the art would have been motivated to create a covalent link between antibiotics, as taught by Truett I, Truett II, Staroske et al., and the reference of Renoud-Grappin et al., which all teach the covalent linkage of antibiotics. Staroske et al., at 4917, para 1, and Renoud-Grappin et al., at p. 208, para 2, teach the covalent linkage of antibiotics to control the geometry or spacing of the antibiotics in their relationship to receptors, for example, in the cell-wall precursor (Staroske et al).

As further indication of applicant's arguments improperly attacking the references individually, the examiner respectfully notes the structural division of applicant's argument (Sections 1-4), wherein the arguments attack the reference of Truett I in Section 1, the reference of Truett II in Section 2. In Section 4, applicant's argument collectively dismisses the references of Boeckh, Renoud-Grappin and Staroske as teaching, for example, nothing that "would have led one of ordinary skill in the art away from the direct teaching in Truett II to employ a three-component antibiotic compound",

(Reply at p. 11, Section 4). This argument attacks Truett II for teaching trimeric compounds, but ignores the fact that Truett I taught dimeric compounds, as in the instantly claimed invention. The examiner respectfully submits that applicant's arguments dismiss any motivation to make the claimed invention by narrowly restricting consideration of each reference in a piecemeal fashion, instead of considering the cited prior art as a whole.

Applicant's argument that that the examiner is "picking and choosing" components and not compositions is not persuasive, because the prior art of Truett II and Boeckh et al. teach combining vancomycin and ceftazidime, either as part of a heterotrimeric antibiotic compound, or in simultaneous administration into a human, respectively.

In regard to applicant's argument that *In re Kerhoven* is inapposite, because the holding of *Kerhoven* requires that the type of combination *not* involve a covalent bond, the examiner finds this argument persuasive, and withdraws it.

Conclusion

5. Claims 41, 43, 49-51 and 53-55 stand finally rejected.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

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PADMASHRI PONNALURI
PRIMARY EXAMINER